Role of muscle stem cells during skeletal regeneration.

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Public Summary:
Although the importance of muscle in skeletal regeneration is well recognized clinically, the mechanisms by which muscle supports bone repair have remained elusive. Muscle flaps are often used to cover the damaged bone after traumatic injury yet their contribution to bone healing is not known. Here, we show that direct bone-muscle interactions are required for periosteum activation and callus formation, and that muscle grafts provide a source of stem cells for skeletal regeneration. We investigated the role of satellite cells, the muscle stem cells. Satellite cells loss in Pax7(-/-) mice and satellite cell ablation in Pax7(Cre) (ERT) (2/) (+) ;DTA(f/f) mice impaired bone regeneration. Although satellite cells did not contribute as a large source of cells endogenously, they exhibited a potential to contribute to bone repair after transplantation. The fracture healing phenotype in Pax7(Cre) (ERT) (2/) (+) ;DTA(f/f) mice was associated with decreased bone morphogenetic proteins (BMPs), insulin-like growth factor 1, and fibroblast growth factor 2 expression that are normally upregulated in response to fracture in satellite cells. Exogenous rhBMP2 improved bone healing in Pax7(Cre) (ERT) (2/) (+) ;DTA(f/f) mice further supporting the role of satellite cells as a source of growth factors. These results provide the first functional evidence for a direct contribution of muscle to bone regeneration with important clinical implications as it may impact the use of muscle flaps, muscle stem cells, and growth factors in orthopedic applications. Stem Cells 2015;33:1501-1511.

Scientific Abstract:
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